# BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

## IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.**

Image

02-26-04

AF/1647





# Appeal Brief

| | |
|---|---|
| Applicant(s) | Walke et al |
| Application # | 09/997,191 |
| Date Filed | November 20, 2001 |
| Title | Novel Human Wnt-Family Protein and Polynucleotides Encoding the Same |
| Attorney Docket # | LEX-0270-USA |
| Group Art Unit | 1647 |
| Examiner | R. DeBerry |

Filed In Triplicate

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Application of: Walke *et al.*

| | | | |
|---|---|---|---|
| Serial No.: | 09/997,191 | Group Art Unit: | 1647 |
| Filed: | 11/20/2001 | Examiner: | R. DeBerry |
| For: Novel Human Wnt-Family Protein and Polynucleotides Encoding the Same | | Attorney Docket No.: | LEX-0270-USA |

# APPEAL BRIEF



**Mail Stop Appeal Brief - Patents**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

## TABLE OF CONTENTS


**APPEAL BRIEF**

Sir:

Appellants hereby submit an original and two copies of this Appeal Brief to the Board of Patent Appeals and Interferences ("the Board") in response to the Final Office Action mailed on July 25, 2003. The Notice of Appeal was submitted on November 25, 2003. This Appeal Brief is timely submitted in light of the concurrently filed Petition for an Extension of Time of one month to and including February 25, 2003, and authorization to deduct the fee as required under 37 C.F.R. § 1.17(a)(1) from Appellants' Representatives' deposit account. The Commissioner is also authorized to charge the fee for filing this Appeal Brief ($165.00), as required under 37 C.F.R. § 1.17(c), to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

Appellants believe no fees in addition to the fee for filing the Appeal Brief and the fee for the extension of time are due in connection with this Appeal Brief. However, should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason related to this communication, the Commissioner is authorized to charge any underpayment or credit any overpayment to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

## I. REAL PARTY IN INTEREST

The real party in interest is the Assignee, Lexicon Genetics Incorporated, 8800 Technology Forest Place, The Woodlands, Texas, 77381.

## II. RELATED APPEALS AND INTERFERENCES

Appellants know of no related appeals or interferences that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

## III. STATUS OF THE CLAIMS

The present application was filed on November 20, 2001, claiming the benefit of U.S. Provisional

Application Number 60/252,361, which was filed on November 21, 2000, and included original claims 1-4. A First Official Action on the merits ("the First Action") was issued on February 20, 2003, in which claims 1-4 were rejected under 35 U.S.C. § 101 as allegedly lacking a patentable utility, claims 1-4 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, and claims 2 and 4 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. In a response to the First Official Action submitted to the Office on May 16, 2003 ("Response to the First Action"), Appellants amended claims 1, 2 and 4, added claims 5 and 6, and addressed the various rejections of claims 1-4.

A Second and Final Official Action ("the Final Action") was issued on July 25, 2003, indicating that the rejection of claims 2 and 4 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite, had been overcome by the amendments and remarks submitted in the Response to the First Action, but maintaining the rejection of claims 1-4 (and newly added claims 5 and 6) under 35 U.S.C. § 101 as allegedly lacking a patentable utility, and under 35 U.S.C. § 112, first paragraph, as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility. In a response to the Final Action submitted to the Office on November 25, 2003 ("Response to the Final Action"), Appellants addressed the various rejections of claims 1-6.

An Advisory Action ("the Advisory Action") was apparently mailed on January 28, 2004, but was never received by Appellants. Based on a telephone message from Appellants' representative David Hibler to Examiner DeBerry on February 24, 2004, Examiner DeBerry agreed to send a copy of the Advisory Action by facsimile, which was received by Appellants on February 25, 2004. The Advisory Action indicated that the rejection of claims 1-6 under 35 U.S.C. § 101 as allegedly lacking a patentable utility, and under 35 U.S.C. § 112, first paragraph, as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, were being maintained. Therefore, claims 1-6 are the subject of this appeal. A copy of the appealed claims is included below in the Appendix (Section IX).

## IV. STATUS OF THE AMENDMENTS

As no amendments have been filed subsequent to the Final Action in this case, Appellants believe that no outstanding amendments exist.

## V. SUMMARY OF THE INVENTION

The present invention relates to Appellants' discovery and identification of novel human polynucleotide sequences that encode a novel protein that shares structural similarity with animal Wnt-family proteins (specification at page 2, lines 3-4), and, more specifically, Wnt-14 (specification at page 20, lines 16-17).

The presently claimed polynucleotide sequences were obtained by aligning cDNAs made from human testis and fetal mRNA and human genomic DNA sequence (specification at page 17, lines 9-11). Three coding single nucleotide polymorphisms were identified in the claimed sequence - specifically, a silent C/T polymorphism at nucleotide position 153 of SEQ ID NO:1; a C/G polymorphism at nucleotide position 946 of SEQ ID NO:1, which can lead to a glutamine or glutamate residue at amino acid position 316 of SEQ ID NO:2; and a C/A polymorphism at nucleotide position 953 of SEQ ID NO:1, which can lead to an threonine or asparagine residue at amino acid position 318 of SEQ ID NO:2 (specification at page 17, lines 12-24).

In addition to the functions associated with Wnt-14, the specification details a number of additional uses for the presently claimed polynucleotide sequences, including in forensic biology (see, for example, the specification at page 3, line 13), in the identification of protein coding sequence (see, for example, the specification at page 3, lines 3-5), in mapping a unique gene to a particular chromosome (see, for example, the specification at page 2, line 5), and in assessing gene expression patterns, particularly using a high throughput "chip" format (see, for example, the specification at page 6, lines 3-6).

## VI. ISSUES ON APPEAL

1. Do claims 1-6 lack a patentable utility?
2. Are claims 1-6 unusable by a skilled artisan due to a lack of patentable utility?

## VII. GROUPING OF THE CLAIMS

For the purposes of the outstanding rejections under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, the claims will stand or fall together.

## VIII. ARGUMENT

### A. Do Claims 1-6 Lack a Patentable Utility?

The Final Action first rejects claims 1-6 under 35 U.S.C. § 101, as allegedly lacking a patentable utility due to not being supported by either a specific and substantial or a well-established utility.

Appellants pointed out in both the Response to the First Action and the Response to the Final Action that a sequence sharing over 99% percent identity at the protein level with the claimed sequence is present in the leading scientific repository for biological sequence data (GenBank), and has been annotated by third party scientists who are *wholly unaffiliated with Appellants* as "Homo sapiens mRNA for WNT14" (Saitoh *et al.*, *Biochem. Biophys. Res. Commun.* **284**:1168-1175, 2001; GenBank accession number AB060283; copies of the alignment, GenBank report, and abstract submitted with the Response to the First Action and the Response to the Final Action provided in **Exhibit A**). Appellants also pointed out that the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. Given this GenBank annotation and scientific publication, there can be **no question** that those skilled in the art would clearly believe that Appellants' sequence is human Wnt-14, **exactly as set forth by Appellants in the specification as originally filed** (at least at page 20, lines 16-17).

Additionally, Appellants pointed out in the Response to the First Action and the Response to the Final Action that the specification as originally filed states that the presently claimed sequence has a role in "cancer" (specification at page 1, line 26), a role that has been **confirmed** by Kirikoshi *et al.* (*Int. J. Oncol.* **19**:1221-1225, 2001; "Kirikoshi"; copy of the abstract submitted with the Response to the First Action and the Response to the Final Action provided in **Exhibit B**), as well as a role in "development" (specification at page 1, line 26), a role that has been **confirmed** by Hartmann and Tabin (*Cell* **104**:341-351, 2001; "Hartmann"; copy of the abstract submitted with the Response to the First

Action and the Response to the Final Action provided in **Exhibit C**). Appellants pointed out that given the **well-established** biological and medical relevance of Wnt-14, those of skill in the art would readily appreciate the utility of the present sequence in numerous applications, as described herein below and in the specification as originally filed. Thus, the present claims **clearly** meet the legal requirements of 35 U.S.C. § 101.

Therefore, Appellants pointed out in the Response to the Final Action that the present situation appears to **directly** track Example 10 of the Revised Interim Utility Guidelines Training Materials (a copy of pages 53-55 of the Revised Interim Utility Guidelines Training Materials, which was submitted with the Response to the Final Action, is provided in **Exhibit D**), which **clearly** establishes that a rejection under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility (see Section VIII(B), below), is not proper when a full length sequence (such as the presently claimed sequence), and has a similarity score greater than 95% to a protein having a known function (such as the nearly 100% identity between the presently claimed sequence and Wnt-14, as discussed above). Therefore, the USPTO examination guidelines also indicate that the present claims clearly meet the requirements of 35 U.S.C. § 101, and thus the rejection of record should be withdrawn.

The Examiner stated that "(t)he specification states that (*sic*) novel human protein (NHP) claimed in the instant application share sequence similarity with mammalian Wnt proteins" (the First Action at page 2), and since "individual members have distinct, and sometimes even opposite, biological activities" (the First Action at page 3), the presently claimed sequence lacks a patentable utility. The Examiner went on to cite articles by Bejsovec (*Curr. Biol.* **9**:R684-R687, 1999) and Martinez Arias *et al.* (*Curr. Opin. Genet. Dev.* **9**:447-454, 1999) to support the position that different Wnt-family member proteins have different functions. However, Appellants pointed out in the Response to the First Action that this argument is **completely irrelevant** to the utility of the sequence claimed in the present application. While Appellants do in fact state that the claimed sequence "shares structural similarity with animal Wnt-family proteins" (specification at page 2, lines 3-4), the specification as originally filed also goes on to further characterize the claimed sequence, not just as a random member of the Wnt-family of molecules, but **specifically as**

**Wnt-14** (specification at page 20, lines 16-17). Therefore, the Examiner's argument in no way supports the allegation that the present claims lack a patentable utility.

The Examiner also cited an article by Skolnick *et al.* (*Trends in Biotech.* **18**:34-39, 2000; "Skolnick") for the proposition that "(k)nowing the protein structure by itself is insufficient to annotate a number of functional classes and is also insufficient for annotating the specific details of protein function" (the First Action bridging pages 2 and 3, emphasis added). However, Skolnick concerns predicting protein function not by overall amino acid homology to other family members, but instead concerns prediction of function based on the presence of certain functional "motifs" present within a given protein sequence. Thus, Skolnick does not apply to the current situation, where overall protein homology is used to assign function to a particular sequence. However, even in the event that Skolnick is applicable, Skolnick itself concludes that "sequence-based approaches to protein-function prediction have proved to be very useful" (Skolnick at page 37), admitting that such methods have correctly assigned function in 50-70% of the cases, thus arguing against the conclusion drawn in the Action. Thus, Skolnick does not suggest a high level of uncertainty in assigning function based on sequence, and thus also does not support the alleged lack of utility.

Furthermore, the **PTO itself** does not require 100% identity between proteins to establish functional homology. As detailed above, Example 10 of the Revised Interim Utility Guidelines Training Materials (see **Exhibit D**) only requires a similarity score greater than **95%** to establish functional homology, **far less** than the nearly **100% identity** between the presently claimed sequence and Wnt-14. Thus, scientific publications that generally assert that very small changes between amino acid sequences can lead to changes in function, or publications describing specific examples of proteins, distinct from Appellants sequence, where a minor change in amino acid sequence has lead to a change in function, have been viewed by the **PTO itself** as irrelevant to the question of utility, and thus do not support the Examiner's allegation that the presently claimed sequence lacks utility. Therefore, the present utility rejection must fail as a matter of policy, and should be withdrawn.

Appellants note for the record that the Examiner seems to accept that the presently claimed sequence is in fact human Wnt-14, as this assertion by Appellants in the Response to the First Action is not

refuted by the Examiner at all in the Final Action. Furthermore, the Examiner acknowledges that Kirikoshi "specifically teaches that WNT 14 mRNA was detected in 7 out of 7 pancreatic cancer lines, 12 out of 12 esophageal cancer lines, 4 out of 4 cervical cancer lines, and 5 out of 7 brain tumor cell lines" and that Hartmann "specifically teach that WNT 14 plays a central role in initiating synovial joint formation" (the Final Action at page 3), but nevertheless questions Appellants assertion of utility because "(t)he instant specification does not disclose a specific cancer cell lines (*sic*) where WNT 14 is exclusively expressed, nor does it disclose a developing skeletal function" (the Final Action at page 3). The Examiner argues that "(t)he specification states that WNT 14 has a role in cancer, however there are many forms of cancer", that "(i)t is well known in the art that cancers such as breast, colon and ovarian have very different etiologies", and that "(t)he specification does not specifically teach the role WNT 14 plays in cancer" (the Final Action at page 3). The Examiner also argues that "(t)he specification fails to teach if development means that WNT 14 affects growth and/or differentiation", and that "(t)he specification fails to teach specific areas of development" (the Final Action at page 4). Appellants respectfully point out that these arguments have **no bearing whatsoever** on the patentable utility of the present claims, for it has long been established that "[I]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works" (*In re Cortright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), quoting *Newman v. Quiqq*, 877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed. Cir. 1989)). See also *Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570, 219 USPQ 1137, 1140 (Fed. Cir. 1983) ("[I]t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests"). Rather, as clearly stated by the Federal Circuit in *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985); "*Cross*") "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Therefore, based on the legal standard for utility, the present claims are clearly in compliance with 35 U.S.C. § 101, and the rejection of record should be withdrawn.

Additionally, regarding the scientific merits of Appellants assertion that the presently claimed sequence has a role in cancer, while Appellants have provided evidence in the form of peer reviewed articles from scientific journals in support of the asserted role of the claimed sequence in cancer, the Examiner has discounted this assertion, stating "tumor cell lines are not equal to tumor tissue", and that

"(t)he cell culturing process alters gene expression and selects subgroups of cells, such that the cultured cells are not (*sic*) longer representative of the diseased tissue" (the Final Action at page 4). The Examiner's provides absolutely **no evidence whatsoever** for the argument that cancer cell lines are not "representative of the diseased tissue", and argument that is **completely** at odds with the understanding of the overwhelming majority of those skilled in the art of cancer research and at least the past 30 years of cancer research, as evidenced by billions of dollars of research funded by the National Cancer Institute and the National Institutes of Health, thousands of peer-reviewed scientific articles, not to mention the fact that the Nobel Prize in Medicine in 1989 was awarded to Dr. J. Michael Bishop and Dr. Harold E. Varmus for their discovery of the cellular origin of retroviral oncogenes, a discovery that was accomplished through the study of cancer cell lines. Presumably, this is why the Examiner provides no scientific support for these arguments. Thus, the Examiner's argument does not even serve to rebut the evidence provided by Appellants concerning the role of Wnt-14 in cancer, and therefore in no way meets the Examiner's burden of overcoming Appellants' evidence of record. Based on sound scientific principles, the present claims clearly meet the requirements of 35 U.S.C. § 101. Therefore, the present utility rejection must fail as a matter of policy, as a matter of science, and as a matter of law, and should be withdrawn.

Although Appellants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), Appellants pointed out in both the Response to the First Action and the Response to the Final Action that in addition to the utility described above, the present invention has a number of other substantial and credible utilities, not the least of which is in "forensic biology", as described in the specification, at least at page 3, line 13. As described in the specification at page 17, lines 12-24, the present sequence defines a number of coding single nucleotide polymorphisms. Specifically: a silent C/T polymorphism at nucleotide position 153 of SEQ ID NO:1; a C/G polymorphism at nucleotide position 946 of SEQ ID NO:1, which can lead to a glutamine or glutamate residue at amino acid position 316 of SEQ ID NO:2; and a C/A polymorphism at nucleotide position 953 of SEQ ID NO:1, which can lead to an threonine or asparagine residue at amino acid position 318 of SEQ ID NO:2. Appellants pointed out that

as such polymorphisms are the basis for forensic analysis, which does not require any information about the function of the encoded protein and is undoubtedly a "real world" utility, the present sequences must in themselves be useful.

The Examiner also questioned this asserted utility, stating "(a) polymorphism does not necessarily mean that the change in amino acid will affect activity or cause a disease or condition" (the Final Action at page 5). Appellants respectfully pointed out that the association of a particular disease with the claimed sequence is not the standard required for utility under 35 U.S.C. § 101 (*In re Brana,* 34 USPQ2d 1436 (Fed. Cir. 1995); "*Brana*"). In *Brana*, the Federal Circuit admonished the Patent and Trademark Office for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. Additionally, Appellants respectfully pointed out that the use of the presently described polymorphisms in **forensic** analysis is **not** disease diagnosis, and **does not require the identification of a specific medical condition**. Thus, the Examiner's argument does not support the allegation that the presently claimed sequence lacks a patentable utility.

The Examiner then states that "identifying people based on the presence or absence of a polymorphism would not define a real world utility" (the Advisory Action at page 2). Appellants hardly know where to begin. Naturally occurring genetic polymorphisms such as that described in the present specification are both the basis of, and critical to, *inter alia*, forensic genetic analysis intended to resolve issues of, for example, identity or paternity. Forensic analysis based on identified polymorphisms such as that identified by Appellants is used to positively identify or rule out suspects in many criminal cases, and in identifying human remains. Paternity determination is based on identified polymorphisms such as that identified by Appellants to positively identify or rule out individuals suspected of fathering a particular child. Therefore, Appellants find the Examiner's position particularly difficult to comprehend. What could be possibly be more substantial and real world than the loss of an individual's freedom or life through incarceration? What could be possibly be more substantial and real world than the positive identification of human remains? What could be possibly be more substantial and real world than the impact, both economic and emotional, that the results of a paternity analysis has on the individuals directly and indirectly

involved? These are all well known and generally accepted uses of identified polymorphisms such as the polymorphism identified by Appellants. Without such identified polymorphisms, the skilled artisan would not be able to carry out such forensic or paternal analyses. Thus, the Examiner's argument in **no way** supports the allegation that the presently claimed sequence lacks a patentable utility.

In fact, **far** from supporting the allegation that the presently claimed sequence lacks a patentable utility, these arguments instead merely reflect how **completely** misinformed the Examiner is about **forensic** analysis. Appellants respectfully pointed out in the Response to the Final Action that **forensic** analysis is used to specifically identify individual members of the human population based simply on the presence or absence of one or more polymorphisms. Appellants reiterate that **forensic** analysis does not require **any information at all** about the ultimate biological function of the encoded protein, or require that the mutation cause a "disease or condition". Using the polymorphic marker as described in the specification as originally field, the skilled artisan can distinguish members of a population from one another without any additional research. In the worst case scenario, this polymorphic marker is useful to distinguish 50% of the population (in other words, the marker being present in half of the population). Appellants point out that the ability of a polymorphic marker to distinguish at least 50% of the population is an inherent feature of any polymorphic marker, and this feature is well understood by those of skill in the art. Appellants note that as a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988). Appellants respectfully point out that all that is required to support this assertion of utility is for the skilled artisan to believe that the presently described polymorphic marker could be useful in forensic analysis. The fact that forensic biologists use polymorphic markers such as that described by Appellants **every day** provides more than ample support for the assertion that forensic biologists would also be able to use the specific polymorphic marker described by Appellants in the same fashion. Therefore, the presently claimed sequence clearly has a substantial and well established utility. The ability to eliminate 50% of the population from a forensic analysis **clearly** is a real world, practical utility.

Furthermore, Appellants submit that the asserted forensic utility is specific precisely because it cannot be applied to just any polynucleotide. In fact, the basis for forensic analysis is the fact that such

polymorphic markers are **not** present in all other nucleic acids, but in fact specific and unique to only a certain subset of the population. Additionally, until a polymorphic marker is actually described it cannot be used in forensic analysis. Put another way, simply because there is a likelihood, even a significant likelihood, that a particular nucleic acid sequence will contain a polymorphism and thus be useful in forensic analysis, until such a polymorphism is actually identified and described, such a likelihood is **meaningless**. Additionally, as set forth in the Response to the First Action and the Response to the Final Action, the requirement for a **specific** utility, which is the proper standard for utility under 35 U.S.C. § 101, should not be confused with the requirement for a **unique** utility, which is clearly an improper standard. As clearly set forth by the Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

Following directly from the quote above, an invention does not need to be the best or only way to accomplish a certain result. Thus, the question of whether or not other nucleic acid sequences are expressed and can be used to assess expression patterns is completely irrelevant to the present utility inquiry. The only relevant question in regard to meeting the standards of 35 U.S.C. § 101 is whether **every** nucleic acid can be so used - and the clear answer to this question is an emphatic **no**. Just because other, or even more useful, polymorphic sequences from the human genome have been described does not mean that the use of the presently described polymorphic markers for forensic analysis is not a specific utility. Furthermore, the requirement for a unique utility is clearly not the standard adopted by the Patent and Trademark Office. If every invention were required to have a unique utility, the Patent and Trademark Office would no longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human diseases, such as cancer, just to name a few particular examples, because the utility of each of these compositions is applicable to the broad class in which each of these compositions falls: all batteries have the same utility, specifically to provide electrical power; all automobile tires have the same utility, specifically for use on automobiles; all golf balls and golf clubs have the same utility, specifically for

use in the game of golf; and all cancer treatments have the same utility, specifically, to treat cancer. However, only the briefest perusal of virtually any issue of the Official Gazette provides numerous examples of patents being granted on each of the above compositions nearly every week. Furthermore, if a composition needed to be unique to be patented, the entire class and subclass system would be an effort in futility, as the class and subclass system serves solely to group such common inventions, which would not be required if each invention needed to have a unique utility. In view of the above standards and "common sense" analysis, there can be little question that the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Furthermore, as the presently described polymorphisms are part of the family of polymorphisms that have a well established utility, the Federal Circuit's holding in *Brana, (supra)* is directly on point. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

*Brana* at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

*Brana* at 1442-1443, citations omitted, emphasis added. As set forth above, the present polymorphisms

are useful in forensic analysis exactly as they were described in the specification as originally filed, without the need for any further research. Even if the use of these polymorphic markers provided additional information on the percentage of particular subpopulations that contain these polymorphic markers, this would not mean that "additional research" is needed in order for these markers as they are presently described in the instant specification to be of use to forensic science. As stated above, using the polymorphic markers as described in the specification as originally field can definitely distinguish members of a population from one another. However, even if, *arguendo*, further research might be required in certain aspects of the present invention, this does not preclude a finding that the invention has utility, as set forth by the Federal Circuit's holding in *Brana*, which clearly states, as highlighted in the quote above, that "pharmaceutical inventions, necessarily includes the expectation of further research and development" (*Brana* at 1442-1443, emphasis added). In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin*, *supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). Once again, as a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, *supra*.

It is important to note that it has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974; "*Langer*"); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971). As clearly set forth in *Langer*:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

*Langer* at 297, emphasis in original. As set forth in the MPEP, "Office personnel must provide evidence

sufficient to show that the statement of asserted utility would be considered 'false' by a person of ordinary skill in the art" (MPEP, Eighth Edition at 2100-40, emphasis added). Absent such evidence from the Examiner, as the skilled artisan would readily understand that the present polymorphic markers have utility in forensic analysis, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Appellants also pointed out in both the Response to the First Action and the Response to the Final Action that as yet a further example of the utility of the presently claimed polynucleotide, as described in the specification at least at page 3, lines 3-5, the present nucleotide sequences have a specific utility in "identification of protein coding sequences". This utility is evidenced by the fact that SEQ ID NO:1 can be used to map the 4 coding exons on human chromosome 1 (present within the human chromosome 1 genomic clone disclosed in GenBank Accession Number AL360269; copies of the alignments and the first page from the GenBank report submitted with the Response to the First Action and the Response to the Final Action provided in **Exhibit E**). Appellants respectfully remind the Board that only a minor percentage (2-4%) of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence, as described above. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). As described in the specification as originally filed at page 3, lines 8-10, the claimed sequences "identify biologically verified exon splice junctions, as opposed to splice junctions that may have been bioinformatically predicted from genomic sequence alone". It is well known that intron/exon boundaries are mutational hot spots, and thus the identification of the actual splice sites is of great utility to the skilled artisan. The specification also details that "sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (*e.g.*, splice acceptor and/or donor sites), *etc.*, that can be used in diagnostics and pharmacogenomics" (specification at page 11, lines 16-21). Appellants respectfully submit that the practical scientific value of biologically validated, expressed, spliced, and

polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. Therefore, the present claims clearly meet the requirements of 35 U.S.C. § 101.

As an additional example of the utility of the presently claimed polynucleotides, as described in the specification at least at page 3, line 5, the present nucleotide sequences also have a specific utility in "mapping a unique gene to a particular chromosome", specifically chromosome 1, as described in the specification as originally filed, at least on page 3, lines 6-7. This is evidenced by the fact that SEQ ID NO:1 can be used to map the 4 coding exons on chromosome 1, as detailed above (see **Exhibit E**). Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of human chromosome 1 that contains the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence. For further evidence in support of Appellants' position, the Board is requested to review, for example, section 3 of Venter *et al.* (*Science* **291**:1304, 2001 at pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Examiner also questioned these utilities, stating that "any chromosome region 1 gene can be used to map the particular area of the chromosome" (the Final Action at page 5). Appellants pointed out in both the Response to the First Action and the Response to the Final Action that this argument is also flawed in a number of respects. First, Appellants respectfully point out that only those small percentage of nucleotide sequences that are located in this region of chromosome 1 can be used in such a manner, and not just "any polynucleotide". Second, the Examiner is clearly confusing the requirements of a **specific**

utility, which is the proper standard for utility under 35 U.S.C. § 101, with the requirement for a **unique** utility, which is clearly an improper standard. The fact that a small number of other nucleotide sequences could be used to map the protein coding regions in this specific region of chromosome 1 does not mean that the use of Appellants' sequence to map the protein coding regions of chromosome 1 is not a specific utility (*Carl Zeiss Stiftung v. Renishaw PLC, supra*; "[A]n invention need not be the best or only way to accomplish a certain result"). The holding in *Carl Zeiss*, and particularly the quote provided above, clearly states that an invention does not need to be the **only way** to accomplish a certain result. Appellants reiterate that the question of whether or not **other** nucleic acid sequences can be used to assess gene expression using DNA chips is **completely irrelevant** to the present utility inquiry. The **only** relevant question in regard to meeting the standards of 35 U.S.C. § 101 is whether **every** nucleic acid can be so used - and the clear answer to this question is an emphatic **no**. Importantly, the holding in *Carl Zeiss* is **mandatory legal authority** that essentially controls the outcome of the present case. This case, and particularly the cited quote, **directly** rebuts the Examiner's argument. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Furthermore, as set forth by Appellants in both the Response to the First Action and the Response to the Final Action, given the well-established role of WNT-14 in cancer and development, the skilled artisan would readily recognize that the present nucleotide sequences also have utility in assessing gene expression patterns using high-throughput DNA chips, as detailed in the specification, at least on page 6, lines 3-6. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776 (**Exhibits F-K**; copies of issued U.S. Patents not provided pursuant to current United States Patent and Trademark Office policy). Given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequence, which is involved in cancer and development, would have great utility in such DNA chip applications. As the present sequence is a specific marker of the human genome, specific ally human chromosome 1 (see above), and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide

sequences would be ideal, novel candidates for assessing gene expression using such DNA chips. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Further evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies that have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company (Rosetta Inpharmatics) was viewed to have such "real world" value that it was acquired by large a pharmaceutical company (Merck) for significant sums of money (net equity value of the transaction was $620 million). Clearly, there can be no doubt that the skilled artisan would know how to use the presently claimed sequences (see Section VIII(B), below), strongly arguing that the claimed sequences have utility. The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, *supra*). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, *Science* **291**:1153, 2001). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years). Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Examiner also questioned this utility, stating that "without a disclosure of a particular disease state in which the claimed polynucleotides are expressed at an altered level or form, it would be impossible to determine what the results of a gene expression monitoring assay mean" (the Final Action at page 6).

However, this argument is misplaced, since the Examiner seems to be requiring knowledge of the results of the expression profiling study before carrying out the study itself. Expression profiling does not require a knowledge of disease states in which expression of the selected nucleic acid is increased or decreased - rather the gene chip indicates which DNA fragments are expressed at greater or lesser levels in two or more particular tissue types. The Examiner stated that "(i)t is unclear what it would mean if a gene chip indicated that a particular DNA fragment is expressed at a greater level in two or more particular tissue types" (the Final Action at page 6). Appellants respectfully pointed out that, for example, the skilled artisan would readily understand the meaning if the presently claimed sequence, which has been detected in a number of cancer cell lines (Kirikoshi, *supra*), was found to be expressed at a greater level in cancer tissue compared to normal tissue. As this is the proper standard for utility, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Regarding whether "significant further research" (the Final Action at page 6) would be required to practice the claimed invention, Appellants pointed out in the Response to the First Action and the Response to the Final Action that nucleic acid sequences such as SEQ ID NO:1 are routinely used by companies throughout the biotechnology sector **exactly** as it is presented in the Sequence Listing, without **any** further experimentation. Appellants respectfully point out that the standard for meeting the requirements of 35 U.S.C. § 101 is **not** whether "further" experimentation is required to practice the claimed invention, but whether "**undue**" experimentation would be required to practice the claimed invention. The widespread use of sequences such as SEQ ID NO:1 throughout the biotechnology industry every day, for example in gene chip applications, strongly argues against such a use requiring "undue experimentation". Appellants reiterate that in assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation" (*In re Angstadt and Griffin*, *supra*), and that the need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art (*In re Angstadt and Griffin*, *supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, *supra*). As a matter of law, it is well settled that a patent need not disclose what is well known in the art (*In re Wands*, *supra*). Furthermore, although information regarding a particular disease state associated

with a particular nucleic acid sequence might make it even more useful in such applications, this does not mean that the presently described nucleic acid sequences lack a specific utility in gene chip applications. Once again, "[A]n invention need not be the best or only way to accomplish a certain result" (*Carl Zeiss Stiftung v. Renishaw PLC, supra*). Thus, the Examiner's argument does not support the alleged lack of utility, and the present claims clearly meet the requirements of 35 U.S.C. § 101.

Regarding the utility requirements under 35 U.S.C. § 101, the Federal Circuit has clearly stated "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 185 F.3d 1364, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 USPQ2d 1401 (Fed. Cir. 1992), emphasis added. Appellants reiterate that *Cross v. Iizuka* (*supra*) states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101" (*Cross* at 748, emphasis added). Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable (*State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 149 F.3d 1368, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (U.S., 1980)). Thus, based on the relevant case law, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Finally, While Appellants are well aware of the new Utility Guidelines set forth by the USPTO, Appellants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Appellants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the

new Utility Guidelines. As examples of such issued U.S. Patents, the Board is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,281 (each of which claims short polynucleotides; **Exhibits L-N**; copies of issued U.S. Patents not provided pursuant to current United States Patent and Trademark Office policy), and recently issued U.S. Patent No. 6,340,583 (which includes no working examples; **Exhibit O**; copies of issued U.S. Patents not provided pursuant to current United States Patent and Trademark Office policy), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section VIII(B), below), Appellants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Appellants understand that each application is examined on its own merits, Appellants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Thus, holding Appellants to a different standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

For each of the foregoing reasons, Appellants submit that the rejection of claims 1-6 under 35 U.S.C. § 101 must be overruled.

### B. Are Claims 1-6 Unusable Due to a Lack of Patentable Utility?

The Final Action next rejects claims 1-6 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by either a clear asserted utility or a well-established utility.

The arguments detailed above in Section VIII(A) concerning the utility of the presently claimed sequences are incorporated herein by reference. As the Federal Circuit and its predecessor have determined that the utility requirement of Section 101 and the how to use requirement of Section 112, first paragraph, have the same basis, specifically the disclosure of a credible utility (*In re Brana, supra*; *In re Jolles*, 628 F.2d 1322, 1326 n.11, 206 USPQ 885, 889 n.11 (CCPA 1980); *In re Fouche*,

439 F.2d 1237, 1243, 169 USPQ 429, 434 (CCPA 1971)), Appellants submit that as claims 1-6 have been shown to have "a specific, substantial, and credible utility", as detailed in Section VIII(A) above, the present rejection of claims 1-6 under 35 U.S.C. § 112, first paragraph, cannot stand.

Appellants therefore submit that the rejection of claims 1-6 under 35 U.S.C. § 112, first paragraph, must be overruled.

## IX. APPENDIX

The claims involved in this appeal are as follows:

1. (Previously Presented) An isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1.

2. (Previously Presented) An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO:2; and

(b) hybridizes to the nucleotide sequence of SEQ ID NO:1 or the complement thereof under highly stringent conditions of 0.5 M $NaHPO_4$, 7% sodium dodecyl sulfate (SDS) and 1 mM EDTA at 65°C and washing in 0.1x SSC/0.1%SDS at 68°C.

3. (Original) An isolated recombinant expression vector comprising a nucleotide sequence encoding the amino acid sequence shown in SEQ ID NO:2.

4. (Previously Presented) A purified protein comprising the amino acid sequence shown in SEQ ID NO:2.

5. (Previously Presented) The recombinant expression vector of claim 3, comprising the nucleotide sequence of SEQ ID NO:1.

6. (Previously Presented) A host cell comprising the recombinant expression vector of claim 3.

## X. CONCLUSION

Appellants respectfully submit that, in light of the foregoing arguments, the Final Action's conclusion that claims 1-6 lack a patentable utility and are unusable by the skilled artisan due to a lack of patentable utility is unwarranted. It is therefore requested that the Board overturn the Final Action's rejections.

Respectfully submitted,

February 25, 2004
Date

David W. Hibler Reg. No. 41,071
Agent for Appellants

LEXICON GENETICS INCORPORATED
8800 Technology Forest Place
The Woodlands, TX 77381
(281) 863-3333

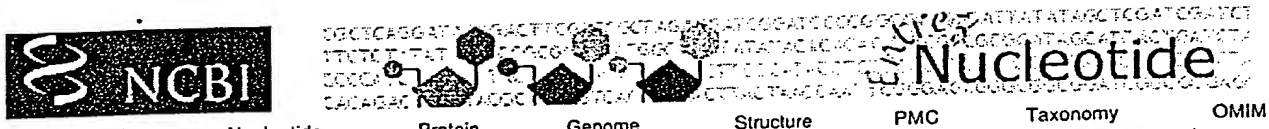
**Customer # 24231**

## TABLE OF AUTHORITIES

### CASES

## STATUTES

```
>AB060283 ACCESSION:AB060283 NID: gi 14530676 dbj AB060283.1  Homo
          sapiens mRNA for WNT14, complete cds
         Length = 1631

 Score =  769 bits (1964), Expect = 0.0
 Identities = 362/365 (99%), Positives = 363/365 (99%)
 Frame = +3

Query: 1    MLDGSPLARWLAAAFGLTLLLAALRPSAAYFGLTGSEPLTILPLTLEPEAAAQAHYKACD 60
             MLDGSPLARWLAAAFGLTLLLAALRPSAAYFGLTGSEPLTILPLTLEPEAAAQAHYKACD
Sbjct: 12   MLDGSPLARWLAAAFGLTLLLAALRPSAAYFGLTGSEPLTILPLTLEPEAAAQAHYKACD 191

Query: 61   RLKLERKQRRMCRRDPGVAETLVEAVSMSALECQFQFRFERWNCTLEGRYRASLLKRGFK 120
             RLKLERKQRRMCRRDPGVAETLVEAVSMSALECQFQFRFERWNCTLEGRYRASLLKRGFK
Sbjct: 192  RLKLERKQRRMCRRDPGVAETLVEAVSMSALECQFQFRFERWNCTLEGRYRASLLKRGFK 371

Query: 121  ETAFLYAISSAGLTHALAKACSAGRMERCTCDEAPDLENREAWQWGGCGDNLKYSSKFVK 180
             ETAFLYAISSAGLTHALAKACSAGRMERCTCDEAPDLENREAWQWGGCGDNLKYSSKFVK
Sbjct: 372  ETAFLYAISSAGLTHALAKACSAGRMERCTCDEAPDLENREAWQWGGCGDNLKYSSKFVK 551

Query: 181  EFLGRRSSKDLRARVDFHNNLVGVKVIKVGVETTCKCHGVSGSCTVRTCWRQLAPFHEVG 240
             EFLGRRSSKDLRARVDFHNNLVGVKVIK GVETTCKCHGVSGSCTVRTCWRQLAPFHEVG
Sbjct: 552  EFLGRRSSKDLRARVDFHNNLVGVKVIKAGVETTCKCHGVSGSCTVRTCWRQLAPFHEVG 731

Query: 241  KHLKHKYETALKVGSTTNEAAGEAGAISPPRGRASGAGGSDPLPRTPELVHLDDSPSFCL 300
             KHLKHKYETALKVGSTTNEAAGEAGAISPPRGRASGAGGSDPLPRTPELVHLDDSPSFCL
Sbjct: 732  KHLKHKYETALKVGSTTNEAAGEAGAISPPRGRASGAGGSDPLPRTPELVHLDDSPSFCL 911

Query: 301  AGRFSPGTAGRRCHRQKTCESICCGRGHNTQSRVVTRPCQCQVRWCCYVECRQCTQREEV 360
             AGRFSPGTAGRRCHR+K CESICCGRGHNTQSRVVTRPCQCQVRWCCYVECRQCTQREEV
Sbjct: 912  AGRFSPGTAGRRCHREKNCESICCGRGHNTQSRVVTRPCQCQVRWCCYVECRQCTQREEV 1091

Query: 361  YTCKG 365
             YTCKG
Sbjct: 1092YTCKG 1106
```




Search Nucleotide for Go Clear

Limits Preview/Index History Clipboard Details

Display default Show: 20 Send to File Get Subsequence

Links

## 1: AB060283. Homo sapiens mRNA...[gi:14530676]

```
LOCUS       AB060283                1631 bp    mRNA    linear   PRI 23-JUN-2001
DEFINITION  Homo sapiens mRNA for WNT14, complete cds.
ACCESSION   AB060283
VERSION     AB060283.1  GI:14530676
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (sites)
  AUTHORS   Saitoh,T., Hirai,M. and Katoh,M.
  TITLE     Molecular cloning and characterization of WNT3A and WNT14 clustered
            in human chromosome 1q42 region
  JOURNAL   Biochem. Biophys. Res. Commun. 284 (5), 1168-1175 (2001)
  MEDLINE   21308441
   PUBMED   11414706
REFERENCE   2  (bases 1 to 1631)
  AUTHORS   Katoh,M.
  TITLE     Direct Submission
  JOURNAL   Submitted (18-APR-2001) Masaru Katoh, National Cancer Center
            Research Institute, Genetics and Cell Biology Section, Genetics
            Division; Tsukiji 5-chome, Chuo-ku, Tokyo 104-0045, Japan
            (E-mail:mkatoh@ncc.go.jp, Tel:81-3-3542-2511, Fax:81-3-3541-2685)
FEATURES             Location/Qualifiers
     source          1..1631
                     /organism="Homo sapiens"
                     /mol_type="mRNA"
                     /db_xref="taxon:9606"
                     /chromosome="1"
                     /map="1q42"
                     /dev_stage="fetus"
     gene            1..1631
                     /gene="WNT14"
     CDS             12..1109
                     /gene="WNT14"
                     /codon_start=1
                     /product="WNT14"
                     /protein_id="BAB61051.1"
                     /db_xref="GI:14530677"
                     /translation="MLDGSPLARWLAAAFGLTLLLAALRPSAAYFGLTGSEPLTILPL
                     TLEPEAAAQAHYKACDRLKLERKQRRMCRRDPGVAETLVEAVSMSALECQFQFRFERW
                     NCTLEGRYRASLLKRGFKETAFLYAISSAGLTHALAKACSAGRMERCTCDEAPDLENR
                     EAWQWGGCGDNLKYSSKFVKEFLGRRSSKDLRARVDFHNNLVGVKVIKAGVETTCKCH
                     GVSGSCTVRTCWRQLAPFHEVGKHLKHKYETALKVGSTTNEAAGEAGAISPPRGRASG
                     AGGSDPLPRTPELVHLDDSPSFCLAGRFSPGTAGRRCHREKNCESICCGRGHNTQSRV
                     VTRPCQCQVRWCCYVECRQCTQREEVYTCKG"
BASE COUNT       293 a    498 c    566 g    274 t
```

```
ORIGIN
        1 ggcgcggcaa gatgctggat gggtccccgc tggcgcgctg gctggccgcg gccttcgggc
       61 tgacgctgct gctcgccgcg ctgcgccctt cggccgccta cttcgggctg acgggcagcg
      121 agcccctgac catcctcccg ctgaccctgg agccagaggc ggccgcccag gcgcactaca
      181 aggcctgcga ccggctgaag ctggagcgga agcagcggcg catgtgccgc cgggacccgg
      241 gcgtggcaga gacgctggtg gaggccgtga gcatgagtgc gctcgagtgc cagttccagt
      301 tccgctttga gcgctggaac tgcacgctgg agggccgcta ccgggccagc ctgctcaagc
      361 gaggcttcaa ggagactgcc ttcctctatg ccatctcctc ggctggcctg acgcacgcac
      421 tggccaaggc gtgcagcgcg ggccgcatgg agcgctgtac ctgcgatgag gcacccgacc
      481 tggagaaccg tgaggcctgg cagtgggggg gctgcggaga caaccttaag tacagcagca
      541 agttcgtcaa ggaattcctg ggcagacggt caagcaagga tctgcgagcc cgtgtggact
      601 tccacaacaa cctcgtgggt gtgaaggtga tcaaggctgg ggtggagacc acctgcaagt
      661 gccacggcgt gtcaggctca tgcacggtgc ggacctgctg gcggcagttg gcgcctttcc
      721 atgaggtggg caagcatctg aagcacaagt atgagacggc actcaaggtg ggcagcacca
      781 ccaatgaagc tgccggcgag gcaggtgcca tctccccacc acggggccgt gcctcggggg
      841 caggtggcag cgacccgctg ccccgcactc cagagctggt gcacctggat gactcgccta
      901 gcttctgcct ggctggccgc ttctccccgg gcaccgctgg ccgtaggtgc caccgtgaga
      961 agaactgcga gagcatctgc tgtggccgcg gccataacac acagagccgg gtggtgacaa
     1021 ggccctgcca gtgccaggtg cgttggtgct gctatgtgga gtgcaggcag tgcacgcagc
     1081 gtgaggaggt ctacacctgc aagggctgag ttcccaggcc ctgccagccc tgctgcacag
     1141 ggtgcaggca ttgcacacgg tgtgaagggt ctacacctgc acaggctgag ttcctgggct
     1201 cgaccagccc agctgcgtgg ggtacaggca ttgcacacag tgtgaatggg tctacacctg
     1261 catgggctga gtccctgggc tcagacctag cagcgtgggg tagtccctgg gctcagtcct
     1321 agctgcatgg ggtgcaggca ttgcacagag catgaatggg cctacacctg ccaaggctga
     1381 atccctgggc ccagccagcc ctgctgcaca tggcacaggc attgcacacg gtgtgaggag
     1441 tgtacacctg caagggctga ggccctgggc ccagtcagcc ctgctgctca gagtgcaggc
     1501 attgcacatg gtgtgagaag gtctacacct gcaagggacg agtccccggg cctggccaac
     1561 cctgctgtgc agggtgaggg ccatgcatgc tagtatgagg ggtctacacc tgcaaggact
     1621 gagaggcttt t
//
```

1: Biochem Biophys Res Commun 2001 Jun 29;284(5):1168-75

Related Articles Link

ELSEVIER SCIENCE FULL-TEXT ARTICLE

# Molecular cloning and characterization of WNT3A and WNT14 clustered in human chromosome 1q42 region.

**Saitoh T, Hirai M, Katoh M.**

Genetics and Cell Biology Section, Genetics Division, National Cancer Center Research Institute, Tsukiji 5-chome, Tokyo, Chuo-ku, 104-0045, Japan.

Human WNT3A and WNT14 cDNAs were cloned and characterized. WNT3A and WNT14 encoded WNT family protein of 352 and 365 amino acids, respectively. The 3.0-kb WNT3A mRNA was moderately expressed in placenta, and the 4.4-kb WNT14 mRNA was moderately expressed in skeletal muscle and heart. Although WNT3A mRNA was not detected in 35 human cancer cell lines, WNT14 mRNA was expressed in gastric cancer cell lines TMK1, MKN7, MKN45 and KATO-III. WNT3A and WNT14 genes, clustered in the head to head manner with an interval of about 58.0 kb, were mapped to human chromosome 1q42 region by fluorescence in situ hybridization. WNT3 and WNT15, clustered in human chromosome 17q21 region, are related genes of WNT3A and WNT14, respectively. WNT3A-WNT14 gene cluster and WNT3-WNT15 gene cluster might be generated due to duplication of ancestral gene cluster, just like WNT10A-WNT6 gene cluster and WNT10B-WNT1 gene cluster. Integration sites of mouse mammary tumor virus (MMTV) are located in the mouse chromosomal regions corresponding to these human WNT gene clusters. These results strongly suggest that unidentified nucleotide motif responsible for susceptibility to recombination might exist within the intergenic regions of these WNT gene clusters. Copyright 2001 Academic Press.

MeSH Terms:

- Amino Acid Sequence
- Chromosome Mapping
- Chromosomes, Human, Pair 1*
- Cloning, Molecular
- DNA, Complementary/analysis
- HL-60 Cells

- Hela Cells
- Human
- K562 Cells
- Karyotyping
- Molecular Sequence Data
- Multigene Family*
- Proteins/genetics*
- Sequence Homology, Amino Acid
- Support, Non-U.S. Gov't

Substances:

- Wnt-3 protein
- WNT14 protein
- Proteins
- DNA, Complementary

Secondary source id:

- GENBANK/AB060284
- GENBANK/AB060283

PMID: 11414706 [PubMed - indexed for MEDLINE]

---

1: Int J Oncol 2001 Dec;19(6):1221-5 Related Articles, Link

# Expression of WNT14 and WNT14B mRNAs in human cancer, up-regulation of WNT14 by IFNgamma and up-regulation of WNT14B by beta-estradiol.

**Kirikoshi H, Sekihara H, Katoh M.**

Genetics and Cell Biology Section, Genetics Division, National Cancer Center Research Institute, Tokyo 104-0045, Japan.

WNT proteins play key roles in carcinogenesis. We have previously cloned and characterized WNT14 and WNT14B/WNT15. WNT14 and WNT3A genes are clustered on human chromosome 1q42, while WNT14B and WNT3 genes are clustered on human chromosome 17q21. Here, we investigated expression of WNT14 and WNT14B mRNAs in human cancer. WNT14 was significantly up-regulated in 1 out of 9 cases of primary breast cancer. WNT14B was not expressed in primary breast, gastric and colorectal cancers. Among 3 human breast cancer cell lines, WNT14 mRNA was expressed in T-47D cells, and weakly expressed in MCF-7 cells. WNT14 mRNA was also detected in 7 out of 7 pancreatic cancer cell lines, 12 out of 12 esophageal cancer cell lines, 4 out of 4 cervical cancer cell lines, and 5 ou of 7 brain tumor cell lines by using cDNA-PCR. These results indicate that WNT14 rather than WNT14B is preferentially expressed in various types of human cancer, such as breast cancer, gastric cancer, and pancreatic cancer. WNT14 mRNA was up-regulated by interferon gamma (IFNgamma), but no by tumor necrosis factor alpha (TNFalpha), in MKN45 cells derived from gastric cancer, while expression of WNT14B mRNA was not affected by IFNgamma and TNFalpha in MKN45 cells. Although expression of WNT14 mRNA was not affected by beta-estradiol in MCF-7 cells, WNT14B mRNA was transiently up-regulated by beta-estradiol in MCF-7 cells. These results indicate that WNT14 is a target gene of IFNgamma in MKN45 cells, and tha WNT14B is a target gene of estrogen in MCF-7 cells.

PMID: 11713592 [PubMed - indexed for MEDLINE]

Display Abstract Show: 20 Sort Send to Text

May 2 2003 16:34:2

1: Cell 2001 Feb 9;104(3):341-51 Related Articles, Link



# Wnt-14 plays a pivotal role in inducing synovial joint formation in the developing appendicular skeleton.

**Hartmann C, Tabin CJ.**

Department of Genetics, Harvard Medical School, 02115, Boston, MA, USA

The long bones of the vertebrate appendicular skeleton arise from initially continuous condensations of mesenchymal cells that subsequently segment and cavitate to form discrete elements separated by synovial joints. Little is known, however, about the molecular mechanisms of joint formation. We present evidence that Wnt-14 plays a central role in initiating synovial joint formation in the chick limb. Wnt-14 is expressed in joint-forming regions prior to the segmentation of the cartilage elements, and local misexpression of Wnt-14 induces morphological and molecular changes characteristic of th first steps of joint formation. Induction of an ectopic joint-like region by Wnt-14 suppresses the formation of the immediately adjacent endogenous joint, potentially providing insight into the spacing of joints.

MeSH Terms:

- Animal
- Bone Development*
- Cartilage/embryology
- Cell Differentiation
- Cells, Cultured
- Chick Embryo
- Chondrocytes/metabolism
- Down-Regulation
- Immunohistochemistry
- In Situ Hybridization
- Joint Capsule/physiology*
- Joint Capsule/embryology*
- Models, Biological
- Molecular Sequence Data
- Proteins/physiology*
- Signal Transduction
- Support, Non-U.S. Gov't

- Support, U.S. Gov't, P.H.S.
- Time Factors

Substances:
- WNT14 protein
- Proteins

Secondary source id:
- GENBANK/M74435
- GENBANK/AF153205

PMID: 11239392 [PubMed - indexed for MEDLINE]

---

Display Citation Show: 20 Sort Send to Text

characterize the protein. A starting material that can only be used to produce a final product does not have a substantial asserted utility in those instances where the final product is not supported by a specific and substantial utility. In this case none of the proteins that are to be produced as final products resulting from processes involving the claimed cDNA have asserted or identified specific and substantial utilities. The research contemplated by Applicants to characterize potential protein products, especially their biological activities, does not constitute a specific and substantial utility. Identifying and studying the properties of the protein itself or the mechanisms in which the protein is involved does not define a "real world" context of use. Note, because the claimed invention is not supported by a specific and substantial asserted utility for the reasons set forth above, credibility has not been assessed. Neither the specification as filed nor any art of record discloses or suggests any property or activity for the cDNA compounds such that another non-asserted utility would be well established for the compounds.

Claim 1 is also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.

**Example 10: <u>DNA Fragment encoding a Full Open Reading Frame (ORF)</u>**

**Specification:** The specification discloses that a cDNA library was prepared from human kidney epithelial cells and 5000 members of this library were

sequenced and open reading frames were identified. The specification discloses a Table that indicates that one member of the library having SEQ ID NO: 2 has a high level of homology to a DNA ligase. The specification teaches that this complete ORF (SEQ ID NO: 2) encodes SEQ ID NO: 3. An alignment of SEQ ID NO: 3 with known amino acid sequences of DNA ligases indicates that there is a high level of sequence conservation between the various known ligases. The overall level of sequence similarity between SEQ ID NO: 3 and the consensus sequence of the known DNA ligases that are presented in the specification reveals a similarity score of 95%. A search of the prior art confirms that SEQ ID NO: 2 has high homology to DNA Ligase encoding nucleic acids and that the next highest level of homology is to alpha-actin. However, the latter homology is only 50%. Based on the sequence homologies, the specification asserts that SEQ ID NO: 2 encodes a DNA ligase.

**Claim 1:** An isolated and purified nucleic acid comprising SEQ ID NO: 2.

**Analysis:** The following analysis includes the questions that need to be asked according to the guidelines and the answers to those questions based on the above facts:

1) Based on the record, is there a "well established utility" for the claimed invention? Based upon applicant's disclosure and the results of the PTO search, there is no reason to doubt the assertion that SEQ ID NO: 2 encodes a DNA ligase. Further, DNA ligases have a well-established use in the molecular biology art based on this class of protein's ability to ligate DNA. Consequently the answer to the question is yes.

Note that if there is a well-established utility already associated with the claimed invention, the utility need not be asserted in the specification as filed. In order to determine whether the claimed invention has a well-established utility the examiner must determine that the invention has a specific, substantial and credible utility that would have been readily apparent to one of skill in the art. In this case SEQ ID NO: 2 was shown to encode a DNA ligase that the artisan would have recognized as having a specific, substantial and credible utility based on its enzymatic activity.

Thus, the conclusion reached from this analysis is that a 35 U.S.C. § 101 rejection and a 35 U.S.C. § 112, first paragraph, utility rejection should not be made.

**Example 11: Animals with Uncharacterized Human Genes**

**Specification:** Kidney cells from a patient with Polycystic Kidney (PCK) Disease have been used to make a cDNA library. From this library 8000 nucleotide "fragments" have been sequenced but not yet used to express proteins in a transformed host cell nor have they been characterized in any other way. The 50 longest fragments, SEQ ID NO: 1-50, respectively, have been used to make transgenic mice. None of the 50 lines of mice have developed Polycystic Kidney Disease to date. The asserted utility is the use of the mice to research human genes from diseased human kidneys. The disease is inheritable, but chromosomal loci have not yet been identified. Neither the absence or presence of a specific protein has been identified with the disease condition.

**Query=** SEQ ID NO:1
(1098 letters)

Sequences producing significant alignments:

| | Score (bits) | E Value |
|---|---|---|
| AL360269.21.1.141703 | 894 | 0.0 |

>AL360269.21.1.141703
Length = 141703

Score = 894 bits (451), Expect = 0.0
Identities = 482/485 (99%)
Strand = Plus / Minus

```
Query: 614   aggtgatcaaggttggggtggagaccacctgcaagtgccacggcgtgtcaggctcatgca 673
              |||||||||||| ||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 68593 aggtgatcaaggctggggtggagaccacctgcaagtgccacggcgtgtcaggctcatgca 68534

Query: 674   cggtgcggacctgctggcggcagttggcgcctttccatgaggtgggcaagcatctgaagc 733
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 68533 cggtgcggacctgctggcggcagttggcgcctttccatgaggtgggcaagcatctgaagc 68474

Query: 734   acaagtatgagacggcactcaaggtgggcagcaccaccaatgaagctgccggcgaggcag 793
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 68473 acaagtatgagacggcactcaaggtgggcagcaccaccaatgaagctgccggcgaggcag 68414

Query: 794   gtgccatctccccaccacggggccgtgcctcgggggcaggtggcagcgacccgctgcccc 853
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 68413 gtgccatctccccaccacggggccgtgcctcgggggcaggtggcagcgacccgctgcccc 68354

Query: 854   gcactccagagctggtgcacctggatgactcgcctagcttctgcctggctggccgcttct 913
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 68353 gcactccagagctggtgcacctggatgactcgcctagcttctgcctggctggccgcttct 68294

Query: 914   ccccgggcaccgctggccgtaggtgccaccgtcagaagacctgcgagagcatctgctgtg 973
              |||||||||||||||||||||||||||||| |||||| ||||||||||||||||||||
Sbjct: 68293 ccccgggcaccgctggccgtaggtgccaccgtgagaagaactgcgagagcatctgctgtg 68234

Query: 974   gccgcggccataacacacagagccgggtggtgacaaggccctgccagtgccaggtgcgtt 1033
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 68233 gccgcggccataacacacagagccgggtggtgacaaggccctgccagtgccaggtgcgtt 68174

Query: 1034  ggtgctgctatgtggagtgcaggcagtgcacgcagcgtgaggaggtctacacctgcaagg 1093
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 68173 ggtgctgctatgtggagtgcaggcagtgcacgcagcgtgaggaggtctacacctgcaagg 68114
```

```
Query: 1094  gctga 1098
              |||||
Sbjct: 68113 gctga 68109
```

```
 Score =  527 bits (266), Expect = e-147
 Identities = 266/266 (100%)
 Strand = Plus / Minus

Query: 351   aggcttcaaggagactgccttcctctatgccatctcctcggctggcctgacgcacgcact 410
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 70993 aggcttcaaggagactgccttcctctatgccatctcctcggctggcctgacgcacgcact 70934

Query: 411   ggccaaggcgtgcagcgcgggccgcatggagcgctgtacctgcgatgaggcacccgacct 470
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 70933 ggccaaggcgtgcagcgcgggccgcatggagcgctgtacctgcgatgaggcacccgacct 70874

Query: 471   ggagaaccgtgaggcctggcagtgggggggctgcggagacaaccttaagtacagcagcaa 530
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 70873 ggagaaccgtgaggcctggcagtgggggggctgcggagacaaccttaagtacagcagcaa 70814

Query: 531   gttcgtcaaggaattcctgggcagacggtcaagcaaggatctgcgagcccgtgtggactt 590
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 70813 gttcgtcaaggaattcctgggcagacggtcaagcaaggatctgcgagcccgtgtggactt 70754

Query: 591   ccacaacaacctcgtgggtgtgaagg 616
              |||||||||||||||||||||||||
Sbjct: 70753 ccacaacaacctcgtgggtgtgaagg 70728
```

```
 Score =  505 bits (255), Expect = e-140
 Identities = 258/259 (99%)
 Strand = Plus / Minus

Query: 95    ggctgacgggcagcgagcccctgaccatcctcccgctgaccctggagccagaggcggccg 154
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||| |
Sbjct: 72111 ggctgacgggcagcgagcccctgaccatcctcccgctgaccctggagccagaggcggctg 72052

Query: 155   cccaggcgcactacaaggcctgcgaccggctgaagctggagcggaagcagcggcgcatgt 214
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 72051 cccaggcgcactacaaggcctgcgaccggctgaagctggagcggaagcagcggcgcatgt 71992

Query: 215   gccgccgggacccgggcgtggcagagacgctggtggaggccgtgagcatgagtgcgctcg 274
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 71991 gccgccgggacccgggcgtggcagagacgctggtggaggccgtgagcatgagtgcgctcg 71932
```

```
Query: 275   agtgccagttccagttccgctttgagcgctggaactgcacgctggagggccgctaccggg 334
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 71931 agtgccagttccagttccgctttgagcgctggaactgcacgctggagggccgctaccggg 71872


Query: 335   ccagcctgctcaagcgagg 353
             ||||||||||||||||||
Sbjct: 71871 ccagcctgctcaagcgagg 71853
```

Score = 190 bits (96), Expect = 1e-45
Identities = 96/96 (100%)
Strand = Plus / Minus

```
Query: 1     atgctggatgggtccccgctggcgcgctggctggccgcggccttcgggctgacgctgctg 60
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 94478 atgctggatgggtccccgctggcgcgctggctggccgcggccttcgggctgacgctgctg 94419


Query: 61    ctcgccgcgctgcgcccttcggccgcctacttcggg 96
             ||||||||||||||||||||||||||||||||||
Sbjct: 94418 ctcgccgcgctgcgcccttcggccgcctacttcggg 94383
```




☐ 1: AL360269. Human DNA sequenc...[gi:21213106]

Links

```
LOCUS       AL360269               141703 bp    DNA     linear   PRI 23-MAY-2002
DEFINITION  Human DNA sequence from clone RP11-192I3 on chromosome 1, complete
            sequence.
ACCESSION   AL360269
VERSION     AL360269.21  GI:21213106
KEYWORDS    HTG.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 141703)
  AUTHORS   Dunn,M.
  TITLE     Direct Submission
  JOURNAL   Submitted (23-MAY-2002) Wellcome Trust Sanger Institute, Hinxton,
            Cambridgeshire, CB10 1SA, UK. E-mail enquiries:
            humquery@sanger.ac.uk Clone requests: clonerequest@sanger.ac.uk
COMMENT     On May 25, 2002 this sequence version replaced gi:20068416.
            During sequence assembly data is compared from overlapping clones.
            Where differences are found these are annotated as variations
            together with a note of the overlapping clone name. Note that the
            variation annotation may not be found in the sequence submission
            corresponding to the overlapping clone, as we submit sequences with
            only a small overlap as described above.
            This sequence was finished as follows unless otherwise noted: all
            regions were either double-stranded or sequenced with an alternate
            chemistry or covered by high quality data (i.e., phred quality >=
            30); an attempt was made to resolve all sequencing problems, such
            as compressions and repeats; all regions were covered by at least
            one plasmid subclone or more than one M13 subclone; and the
            assembly was confirmed by restriction digest. The following
            abbreviations are used to associate primary accession numbers given
            in the feature table with their source databases: Em:, EMBL; Sw:,
            SWISSPROT; Tr:, TREMBL; Wp:, WORMPEP; Information on the WORMPEP
            database can be found at
            http://www.sanger.ac.uk/Projects/C_elegans/wormpep This sequence
            was generated from part of bacterial clone contigs of human
            chromosome 1, constructed by the Sanger Centre Chromosome 1 Mapping
            Group.  Further information can be found at
            http://www.sanger.ac.uk/HGP/Chr1
            RP11-192I3 is from the library RPCI-11.1 constructed by the group
            of Pieter de Jong. For further details see
            http://www.chori.org/bacpac/home.htm
            VECTOR: pBACe3.6.
FEATURES             Location/Qualifiers
     source          1..141703
                     /organism="Homo sapiens"
                     /mol_type="genomic DNA"
```